

UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner: SZNAIDMAN, Marcos L. Art Unit: 1628

Re: Application of: KIM, Myung-Hwa, et al.

Serial No.: 10/562,615

Filed: July 27, 2006

For: **TRICYCLIC DERIVATIVES OR
PHARMACEUTICALLY SALTS THEREOF, THEIR
PREPARATIONS AND PHARMACEUTICAL
COMPOSITIONS CONTAINING THEM**

Confirmation No.: 6138

DECLARATION UNDER 37 CFR § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Sir:

I, KIM, Myung-Hwa, declare and state:

1. My educational background includes a Ph. D. in medicinal chemistry from , Johannes Gutenberg University at Mainz in Germany; a study in a M.S. program in Pharmacy Johannes Gutenberg University at Mainz in Germany; and a B.S. Degree in Pharmacy from Duksung Women's University, in Seoul, KOREA. My postdoctoral work was in the field of medicinal chemistry at Korea Institute of Science and Technology in Seoul/Korea.

2. I presently hold the position of Division of New Drug Development, Jeil Pharmaceutical Co., Ltd. in Yongin-City, KOREA.

3. My expert opinion and conclusions, as set forth in this Declaration, are based upon my familiarity with the invention taught by the above-identified patent application, for which I am a co-inventor, together with my expertise and experience in the field of medicinal chemistry and

pharmacology as evidenced by my more than 19 publications 20 patents and 21 years of design and development of new drug candidates for various therapeutic fields for chemistry, pharmacology, toxicology.

4. My further professional experience and publications are summarized in my Curriculum Vitae, which is attached as Exhibit A.

5. I have read and understood the Examiner's Office Action of May 10, 2011, which rejects claims 12-13 and 6-21, as possibly being obvious over previously published documents. In this regard, the Examiner relied on two references: Kim et al. (WO 02/100824) and Patani et al. (Chem. Rev. (1996) 96:3147-3176). I have also read these references and understand their respective disclosures. Specifically, I understand that the Examiner considers that Fluorinated compound of the present invention is an obvious variation of non-fluorinated compounds, such as Compound 6 of Kim et al.

6. I believe that I am well-qualified as an expert in the field to analyze these references. I further believe that I am well-qualified as an expert in the field to render an opinion concerning whether the claimed compounds, especially fluorinated compounds, not only express superior therapeutic efficacy but also low toxicity compared to the compounds of the references, especially those in Kim et al.

7. To provide superior toxicity profile, such as reduced toxicity, we have subjected two compounds of the instant invention (Examples 8 and 12) for single and multiple dose study using ICR female/male mice, 3 per group. The compounds were administered orally and Compound 8 was subjected to two different dose schedules: 150, 300, 600, and 1,200 mg/kg bolus and 0, 10, 30, 100, and 300 mg/kg daily for 7 days, followed by monitoring of survival rate for two weeks. Compound 12 was subjected to 150, 300, 600, and 1,200 mg/kg bolus administration, followed by monitoring for one week. Several toxicity profile factors were monitored, in both studies, such as normal activity level, weight loss, and pathological analysis upon necropsy. In addition to observation, LD50 (lethal dose to kill 50% of the test animal) was calculated based on the result.

8. Observation:

1) Death:

There was no death in all dose groups of Example 8 in bolus group. One death from each of the following group was observed: Example 8 on day 10 in male for daily dose of 300 mg, Example 8 on day 8 in female for daily dose of 300 mg. Example 12 in male and female for bolus dose of 1,200 mg.

2) Other GI track response: In all groups, some mild irritation around.

(Ex 8) Diarrhea, soft stool and soiled anal region were detected in single dosed groups and multiple dosed groups. Among multiple dosed groups, anal edema was detected in male group on day 7 after administering with 100 and 300 mg/kg, and in female group on day 6 after administering with 300 mg/kg. After finishing the administration, they were slowly recovered.

(Ex 12) Among the major symptoms including diarrhea, soft stool, soiled anal region, rough fur, voluntary motion decrease and abdominal distension, the frequencies of diarrhea, soft stool, and soiled anal region were more severe in higher dose. These symptoms were considered by test material. Especially, rough fur, voluntary motion decrease and abdominal distension were detected only in higher dose groups, which were considered as the symptoms by test material.

3) Weight Loss:

(Ex 12) Compared to vehicle control group, the weight loss was observed in male and female of the 600 mg/kg on day 1, in male of 1,200 mg/kg until day 7 and female of 1,200 mg/kg until day 3.

(Ex 8) Compared to vehicle control group, weight loss was observed in single bolus group on day 1 and 3 but there was no significant difference. Weight was decreased in male of 300 mg/kg with repeated dose group on day 7 and they showed significant differences ($p < 0.01$). Also, weight was decreased in female of 300 mg/kg with repeated dose group on day 7 but they showed no significant differences.

4) Necropsy:

(Ex. 12) In necropsy finding, retention in stomach and intestine was observed in dead animals. This finding is considered by test material.

(Ex.8) In necropsy finding, gas retention was observed in stomach of alive animals and liquid retention in intestine of dead animals. This finding is considered by test material.

5) From the study, LD₅₀ of Examples 8 and 12 were found as presented in the table below compared to Compound 6 of Kim et al.

	Compound	Oral administering toxicity (LD ₅₀)
Present invention	Example 8	1200 mg/kg
	Example 12	1000 mg/kg or above
Kim et al.	Compound 6	Approx. 10 mg/kg (See Table 7 of Kim et al.)

From the result, it is clear that the LD₅₀ by one oral administration of Examples 8 and 12 of the present invention hovers around 1000 mg/kg, which is considered to be very safe compound especially considering their anti-cancer efficacy presented in the application. Also, the result significantly exceeds the oral administering toxicity (i.e., 10 mg/kg) of Compound 6 of Kim et al. found in the reference.

9. In my opinion, Compounds from Examples 8 and 12 of the present application, employed in the present study, have a significantly improved toxicology profile over Compound 6 of Kim et al.

10. Considering the efficacy data provided in the application and toxicity profile as presented in this Declaration, we believe the compounds of Formula (I) of the present invention is not a mere variation of the compounds of Kim et al.

11. The undersigned hereby declare that all statements made herein based upon knowledge are true, and that all statements made based upon information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false

statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

20. September 2011

Date

Myung-Hwa Kim

Signature: KIM, Myung-Hwa